#9/B JRP 7/18/95

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Barberich et al.

Serial No.: 08/335,480 Group Art Unit: 1205

Filed: November 7, 1994 Examiner: Henley III, R.

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE (R)-ALBUTEROL

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, June 9, 1995.

Philip E. Hansen
Agent for Applicant
Reg. No. 32,700

Date of Signature: June 9, 1995

Assistant Commissioner for Patents
Washington, D.C. 20231

RESPONSE UNDER 37 C.F.R 1.111

Dear Sir:

This is in response to the Official Action of March 9, 1995 (Paper No. 7). The three-month period for response expires June 9, 1995; this response is therefore timely filed.

AMENDMENTS

Please amend the application as follows:

In the specification:

Page 1, line 2 (following the title and preceding the "Description"), please delete "This application is a continuation of application Serial No. 08/163,581, filed 12/7/93." and replace with

P:\USERS\BPP\07010270.XES
June 9, 1995

A

--Cross Reference to Related Applications

This application is a continuation of application Serial No. 08/163,581, filed December 7, 1993 and now U.S. Patent 5,362,755, which was a continuation of application Serial No. 07/896,725, filed June 9, 1992, now abandoned, which was a continuation of application Serial No. 07/461,262 filed January 5, 1990, now abandoned.--

In the claims:

Cancel claims 5, 7 and 9-12.

Amend claims 1 and 6 as follows:

1. (once amended) A method of treating an acute attack of asthma [in an individual with albuterol], while reducing side effects associated with the acute administration of racemic albuterol, comprising administering to [the] an individual suffering from an acute attack of asthma a quantity of an optically pure R(-) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects, said R isomer being substantially free of its S(+) isomer.

6. (once amended) A method of treating an acute attack of asthma [in an individual with albuterol], while reducing side effects associated with the acute administration of racemic albuterol, comprising administering to [the] an individual suffering from an acute attack of asthma a quantity of an optically pure R(-) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects, and at least one additional drug selected from the group consisting of bronchodilators, antihistamines and analgesics.

REMARKS

The specification has been amended to clarify that it claims priority of the great grandparent application and to fully characterize the intervening applications. The claims have been amended to clarify the invention sought to be patented in the present application. The claims have been amended so that they parallel the allowed claims in parent application Serial No. 08/162,581 (Now U.S. Patent 5,362,755); the sole difference is that the claims in the parent related to reducing side effects upon chronic administration and the instant claims relate to reducing side effects associated with acute administration. Support for the amendment is found on page 4, line 4 to line 13. The reference to the administration of albuterol to an individual "after onset of asthma to reduce breathing difficulty" (line 7) reflects acute medication, whereas the reference to prophylactic treatment (line 10) relates to chronic therapy.

Claims 1-12 were presented in the application as filed. Claims 5, 7 and 9-12 are canceled by amendment above. Claims 1-4, 6 and 8 are therefore pending in the application.

In the Office Action of March 9, 1995, all of the claims were rejected as obvious over Muittari et al. (CK) in view of Brittain et al. (CB), Hawkins et al. (CD) and Hartley et al. (CC). The rejection is traversed. Applicants' position on what the cited art fairly teaches was presented in their Preliminary Remarks, submitted December 7, 1993, in the parent case and reiterated below.

The Muittari reference is directed to a comparison of bronchodilator effects of racemic albuterol and drug combinations incorporating racemic albuterol. The reference does not teach or suggest the use of an optically pure isomer of albuterol either alone or in combination. Arguably, the

reference teaches away from the use of a single isomer to reduce side effects: it states, "a combination of salbutamol [albuterol] and hydroxyzine seems, therefore, to be one rational means of treating asthma with fewer side effects than the salbutamol-hydroxyzine-theophylline mixture, but still about the same effectiveness." Thus, the goal of the reference appears to be to lower the side effects associated with albuterol. However, rather than separate the enantiomers and use one enantiomer, as taught by applicants, (which the Examiner has alleged would be obvious) the authors turned instead to modulating components of the mixture.

Brittain et al. show that both enantiomers and the racemic mixture of albuterol are very selective for β_2 receptors, but the isomeric activity ratio of R- and S-albuterol on isolated tracheal muscle (β_2) vs atrial muscle (β_1) is "impossible to calculate...because the isomers are virtually inactive on this tissue." The potency ratio of R(-) vs racemic albuterol in β_2 receptors as measured by acetylcholine-induced bronchospasm in anesthetized guinea pigs is 1.28, in acetylcholine-induced pulmonary resistance in anesthetized dogs is 2.3 and on isolated guinea pig trachea is 0.90 (i.e. the racemate is 1.1 times as potent as the R isomer). Thus, from a study of the Brittain reference one may conclude nothing definitive regarding either the selectivity of R vs racemic or of the potency of R vs racemic.

Hartley and Middlemiss teach that both isomers and the racemic mixture of albuterol act on β_2 receptors rather than β_1 receptors. The effects of the R isomer and the racemic mixture are equiactive on β_2 receptors of the intact guinea pig trachea and indeed the racemate is reported to be 1.5 times as potent as the R isomer. There is no clear teaching with

regard to selectivity between β_1 and β_2-receptors, which might indicate the potential for side effects. Thus no conclusion can be drawn from Hartley and Middlemiss as to whether the R isomer would enjoy any advantage over racemic albuterol in terms of side effects.

Hawkins et al. found that the R enantiomer was 2.15 times as potent as the racemate. They did not examine any tissue other than guinea pig trachea so that no conclusion relating to relative selectivity could be drawn.

Putting all this together: Hawkins et al. appear to indicate that the R isomer is about twice as potent as the racemate (which merely indicates that the S-isomer is inert); Hartley et al. teaches that the racemate is about 1.5 times as potent as the R isomer (which would indicate that the S-isomer has some therapeutic potency); Brittain et al. indicates that one or the other isomer is more potent, depending on the test. There is a certain lack of agreement among the references concerning the relative potency of the R isomer and the racemate, and the person of ordinary skill in the art would be, at least, confused by the cited references, but by discarding all the data that don't conform to the desired conclusion, it is possible to conclude that the R isomer may enjoy a theoretical twofold potency advantage over the racemate. The Examiner reaches this conclusion with respect to the teachings of the references in the Office Action of March 9. For the sake of the arguments below, applicants assume that the R enantiomer is twice as potent as the racemate, although they question whether the cited references establish this.

As long as S-albuterol is totally inert ballast, a twofold potency enhancement is of no practical consequence: a process for the resolution of racemic albuterol would

inevitably produce R-albuterol in less than 50% yield, whereas the use of the racemic albuterol would, at worst, provide 50% of the potency of the pure R. Thus there is nothing to be gained by resolving the racemate. As stated in European patent application 256586 (page 2, line 8), "a major reason for the continued use of mixtures of stereoisomers is that the cost of separation of the stereoisomers exceeds the potential advantage of a possible increase in activity."

Testa and Trager [Chirality 2, 129-133 (1990)] have created a decision tree to aid in deciding whether to develop a racemic pharmaceutical or a single enantiomer. A copy of the reference is submitted herewith as Exhibit A. If it were the case that it would always be obvious to develop a single enantiomer, there would be no need for Testa and Trager's decision tree. As they make clear, the mere fact that enantiomers exist is not justification for administering a single enantiomer; moreover, even the fact that one of the two enantiomers is more potent is not determinative. They state

> "While it is abundantly clear that a racemic mixture must be considered as the mixture of two pharmacologically distinct entities, it is also clear that this view, in and of itself, does not infer any value judgement. Such judgment awaits the light of scientific fact and it is only in this context that any decision as to develop a racemate or a eutomer as a new drug is convincingly founded."

The scientific facts referred to by Testa and Trager as they relate to albuterol were shown in the cited references to result in the judgment that the racemate was the proper entity to develop, and although both enantiomers have been known in the art for 24 years, neither has ever been developed as a pharmaceutical.

In the Office Action of March 9, 1995, the Examiner cited *In re Adamson*. Although *In re Adamson* suggests that optical isomers *per se* are normally obvious over the corresponding known racemate, the decision should not be extended to stand for the proposition that a new method for using an isomer is unpatentable, particularly where, as here, the method unexpectedly provides an improved therapeutic ratio. [See, for example, U.S. patent 4,851,444 (Exhibit B), issued 29 years after Adamson, whose claims cover a method for using S-(+)-ibuprofen for onset-hastened analgesia, although (S)-ibuprofen *per se* was well known at the time of filing the application for a new use.]

In the present case, applicants claims relate to a new use, namely a method for treating asthma while simultaneously reducing side effects associated with the administration of racemic albuterol. The unexpected diminution in side effects when the pure R isomer of albuterol is administered is the basis of the instant application, and is not suggested by any of the references. [That the references singly and in combination suggest that there would be no diminution of side effects is fully argued in the Declaration Under 37 C.F.R. 1.132 of February 8, 1993, by Dr. Gunnar Aberg, submitted with the Response of February 10, 1993, in the grandparent case 07/896,725. A copy of that declaration is enclosed herewith as Exhibit C, and attention is drawn to page 5.] References do exist that suggest an advantage to R-albuterol over racemic albuterol for the reduction of side effects [Morley et al. and Chapman et al., of record in the parent case], but they were published more than a year after the priority date of the instant application, and merely add support to the patentability of the claims in the parent '581 application.

In *Adamson*, the CCPA held that in establishing that one isomer was more potent, the applicants had "done no more than what is suggested by the prior art and have ascertained no more than what would be expected by one skilled in the art". In the present case, applicants have shown that the resolution of the racemate and the use of R-(-)-albuterol substantially free of its S-isomer would provide therapy for asthma while simultaneously reducing side effects. This is considerably more than is "suggested by the prior art"; on the contrary, the art suggests that there would be no reduction in side effects. In contradistinction to the premise in *Adamson*, where presumably the art is silent, in the present case the art teaches away. Thus, the decision in *Adamson* is not controlling in this situation.

Against this background in the parent case, Examiner Henley concurred with applicants that the use of R-albuterol to treat asthma while avoiding the side effects associated with chronic administration was nonobvious. However, he did not believe that applicants' showings were sufficient to support that portion of the claimed subject matter that related to side effects associated with acute administration of racemic albuterol. For that reason he would only allow claims restricted to chronic administration. Applicants now seek to complete the original breadth of the claims, and in support thereof, submit herewith the Declaration Under 37 C.F.R. 1.132 of Dr. Dean A. Handley.

The declaration of Dr. Handley establishes that by removing the S enantiomer one maintains the bronchodilatory effects exhibited by racemic albuterol for acute therapy of asthma attacks, while simultaneously avoiding or mitigating the major side effect observed in acute therapy. To summarize briefly, Dr. Handley shows that R-albuterol produces potent

and acute bronchodilation in stable asthmatic patients. The onset of action is rapid and persists for 3 hours. R-Albuterol provides acute, symptomatic treatment and relief for conditions of asthma and bronchitis. S-albuterol is essentially without effect.

On the other hand, both individual enantiomers and racemic albuterol induce sustained tremors in animals. The preclinical observations on the relative abilities of the albuterol enantiomers to provoke tremors upon single dose, acute administration were quite unexpected. Skeletal muscle tremor is one of the most common side effects of ordinary doses of all marketed β_2-agonists. The studies reported in the declaration demonstrate that, unlike the R enantiomer, the tremorigenic liability associated with the S enantiomer is not balanced by a corresponding efficacy in producing bronchodilation. This presents a clear rationale for employing the pure R enantiomer, substantially free of the S enantiomer, in acute therapy of asthma attacks. By removing the S enantiomer, one maintains the bronchodilatory effects of racemic albuterol while providing only half the tremorigenic dose.

In light of the foregoing amendments, declaration and explanation, it is believed that the claims are allowable, and reconsideration of the rejection is respectfully requested.

The Office Action of March 9, 1995, also included a rejection of claims 1-8 under the judicially created doctrine of double patenting of the obviousness type. In the parent case, over which the unamended claims were rejected, the Examiner took the position that applicants' declarations were sufficient to establish the unexpected utility of R-albuterol in avoiding side effects associated with chronic therapy, but not those side effects associated with acute therapy.

Implicit in the earlier requirement to limit the claims to chronic therapy was the assumption that the fact that effects were demonstrated in chronic therapy did not suggest that those same advantages would be observed in acute therapy. If advantages in chronic therapy would not predict advantages in acute therapy, applicants believe that by amending the claims to limit them to side effects associated with acute therapy, they have now eliminated the overlapping obvious subject matter, and the double patenting obviousness rejection would no longer apply.

Respectfully submitted,

Philip E. Hansen
Agent for Applicants
Registration No. 32,700

Dated: June 9, 1995

HESLIN & ROTHENBERG, P.C.
5 Columbia Circle
Albany, New York 12203-5160
Telephone: (518) 452-5600
Facsimile: (518) 452-5579

Chirality 2(1990) 129-133

CHIRALITY 2:129–133 (1990)

Exhibit A

Racemates Versus Enantiomers in Drug Development: Dogmatism or Pragmatism?

BERNARD TESTA AND WILLIAM F. TRAGER

Institut de Chimie thérapeutique, Ecole de Pharmacie, Université de Lausanne, CH-1005 Lausanne, Switzerland (B.T.); and Department of Medicinal Chemistry, School of Pharmacy, University of Washington, Seattle, Washington 98195 (W.F.T.)

KEY WORDS: chiral drugs, racemates, eutomers, distomers, pharmacodynamic enantioselectivity, pharmacokinetic enantioselectivity, enantioselective interactions

INTRODUCTION

Of the many drugs that are chiral, most display marked enantioselectivity in their therapeutic activities, the more active and lesser active enantiomers being termed eutomers and distomers, respectively.[1,2] Yet a significant proportion of these chiral drugs, in fact the large majority of those of synthetic origin, are marketed as racemic mixtures. This situation has, in recent years, led to increasing uneasiness about racemic drugs "containing 50% impurity."[3,4]

While there are indeed cases in which one enantiomer is known to be harmful (and has not found its way into marketed medicines), a number of distomers appear to be nothing more than inert ballast and their removal has not been deemed necessary. Two extreme attitudes are thus conceivable, namely a myopic *laissez-faire* and a rigid prohibition of racemates. In the present discussion, we want to take issue with such extreme attitudes and point to a middle way based on scientific arguments rather than administrative dogmatism or commercial shortcuts. The pragmatic procedures we outline and advocate are certainly not rapid and cheap ones, yet they should inspire, we believe, all drug scientists whose goal is optimal pharmacotherapy.

ASKING THE RIGHT QUESTIONS

The decision whether to develop and market the eutomer or the racemate of a given chiral drug should belong to scientists only and be based primarily on scientific evidence. To obtain the latter, many studies will have to be planned and conducted, and these begin by asking the right questions. [illegible]

Our goal is first to suggest a number of relevant and gainful questions whose answers can contribute to an enlightened decision on our central issue. When such questions are formulated, it becomes clear that they should be ordered logically and not approached randomly. In fact, we go as far as believing that they can be elaborated into logical decision schemes (decision trees).

Figure 1 offers such a decision tree, which is in fact a more elaborate and mature version of previously published schemes.[3,5] It is based on the questions we deem right, and it orders them into sequences that make sense. Before discussing and exemplifying these questions, some limitations of decision trees must be spelled out:

1. The specific questions which form the raw materials of decision trees can have different degrees of relevance and some may even be largely irrelevant. In contrast, important questions may have been overlooked. Continuous update is thus necessary.
2. The logical sequences of questions may be found to be suboptimal, again calling for an evolution of the decision tree. In a more fundamental perspective, the optimal decision tree, if the concept of optimality has any meaning at all in this context, may be one of high multidimensionality. Tractable decision trees will necessarily be simplified ones.
3. As will be discussed later, a decision tree currently implies Aristotelian logic, i.e., yes–no answers. Yet fuzzy answers may well be the rule rather than the exception in biology and pharmacology, and the incorporation of fuzzy logic into decision trees must be encouraged.
4. Since selective interactions may occur at several levels and be modified by a number of physiological states, a decision tree may perhaps be impossible to construct for a given drug (M. Simonyi, private communication, 1989).

CONFIGURATIONAL STABILITY?

As trivial as it may seem, this simple question should be answered before embarking on time-

Received for publication April 13, 1990; accepted April 30, 1990.
Address reprint requests to B. Testa at the address given above.

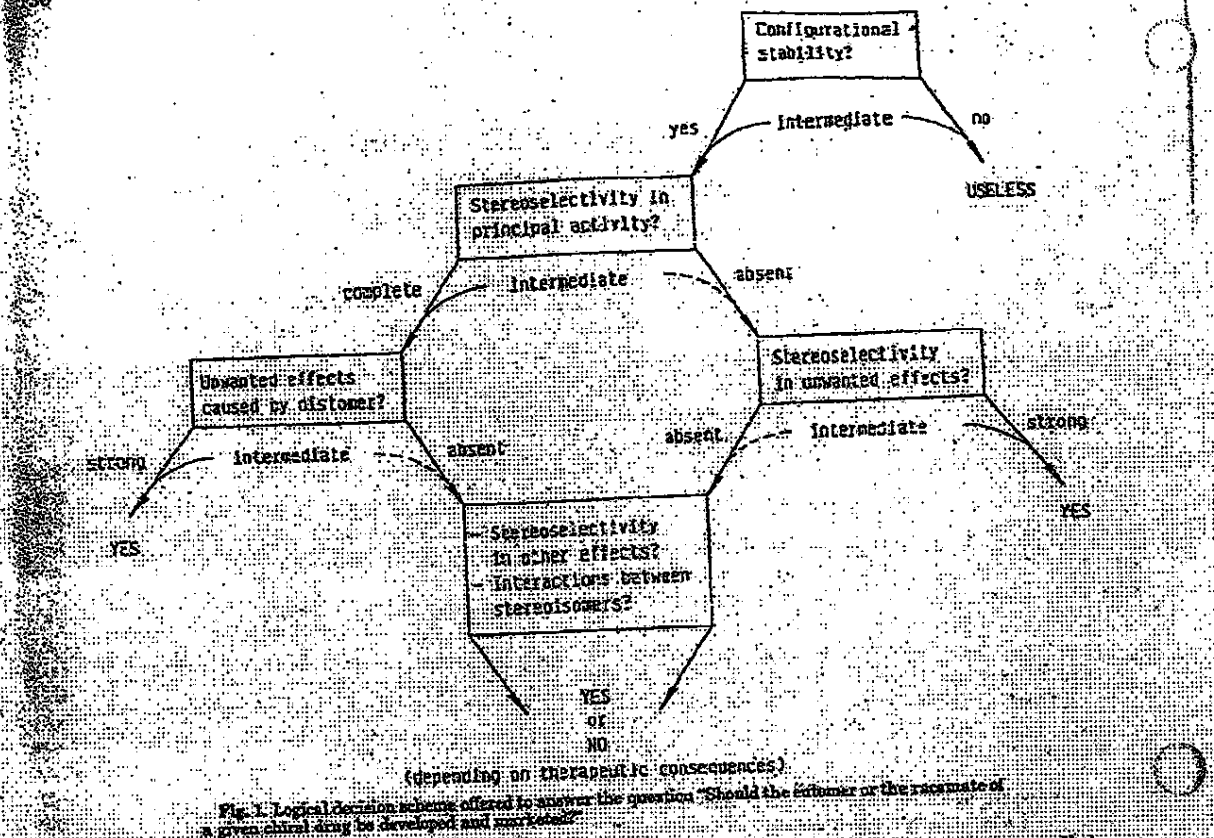


Fig. 1. Logical decision scheme offered to answer the question "Should the distomer or the racemate of a given chiral drug be developed and marketed?"

consuming pharmacokinetic and pharmacodynamic studies. Cases indeed exist of drugs whose enantiomers interconvert readily due to their element of chirality being unstable. Asymmetrically substituted tertiary amines fall into this group,[7] but such examples are too well known to deserve discussion. In contrast, not all asymmetrically substituted carbon atoms are configurationally stable. A representative drug is oxazepam (I), whose asymmetric carbon-3 undergoes rapid inversion. From the work of Aso et al.,[8] the rate constant of racemization of oxazepam in the pH range 6–8 at 20°C can be estimated to be about 0.05 min^{-1}, corresponding to a $t_{1/2}$ of about 14 min. A later study,[9] while ignoring the work of Aso et al., reports confirmatory results presumably obtained at room temperature.

Due to this lack of configurational stability, it is obvious to all that the resolution of oxazepam for therapeutic purposes is completely pointless. Other cases, however, may not be so clear-cut, witness amfegramone (II). The $^1H/^2H$ exchange of the methine proton, which was taken as a mechanistic model of the reaction of racemization, was found to be a first-order process with a $t_{1/2}$ of 15 h at 37°C in D_2O buffered to a pD value of 7.4.[10] This value, which is longer than the biological half-life of the drug in humans (1.5–2h), is nevertheless relatively short and exemplifies what Figure 1 classifies as "intermediate configurational stabilities."

In contrast to drugs with poor or intermediate configurational stability, cases are known of drugs whose enantiomers are far more stable than would be expected by non-stereochemists. This characteristic is usually accompanied by the presence of axial or planar chirality rather than central chirality. A most telling and recently uncovered example is that of telenzepine, whose enantiomers are shown in Figure 2. The energy of activation of racemization was found to be 35 kcal/mol,[11] implying essentially complete stability under physiological conditions of temperature and pH.

STEREOSELECTIVITY IN PRINCIPAL ACTIVITY

This question is certainly a key one in our context. By principal activity, we mean the mechanism of action which contributes predominantly to the therapeutic effect(s), other favourable (wanted) activities being discussed later. According to Pfeiffer's rule,[12] there is an inverse relationship between the effective dose of a chiral drug and the ratio of activity of its enantiomers (stereoselectivity, stereoselective index, eudismic index). This quite approximate rule has been put on more quantitative grounds and repeatedly (neglecting a few exceptions) confirmed by eudismic analysis.[13–15] As a consequence, modern highly effective drugs acting on receptors, enzymes, and other specific sites tend to display very high or even apparently complete stereose-

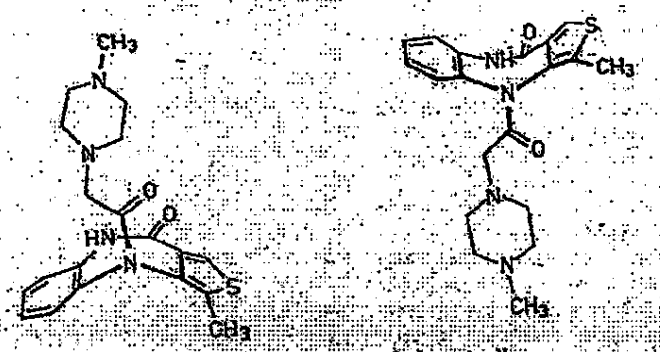


Fig. 2. The two enantiomers of telenzepine.[21]

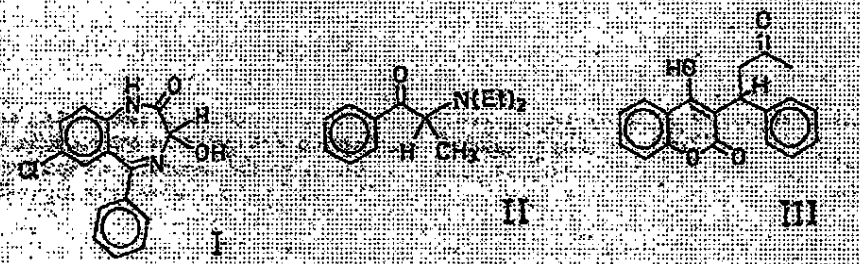
activity and a decision at this branching point of the decision tree can easily be made. Note however that the higher the true stereoselective index, the greater the error in the apparent stereoselective index as a result of incomplete resolution.[14]

However, not all chiral drugs allow such a straightforward answer. First, many cases exist of drugs displaying little or no stereoselectivity, for example, some barbiturates and other antiepileptic agents. Intermediate cases also exist and are characterized by moderate stereoselective indices. For example, in the human the S-enantiomers of both warfarin (III) and phenprocoumon (IV) are five to six times more potent as hypoprothrombinemic agents than the corresponding R-enantiomers.[15,16]

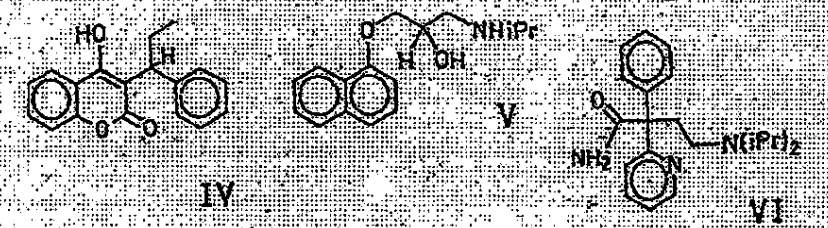
But what about drugs that display a reversal in stereoselectivity depending on dose or pharmacokinetic factors? Consider for example the effects of some analogs of clofibric acid on rat skeletal muscle chloride channels.[17] While the (−)-S-enantiomers produced only a decrease of chloride conductance with increasing concentration until an almost complete block was reached, the (+)-R-enantiomers increased conductance at low concentrations and moderately decreased it at high concentrations. In other words, enantiomers elicited qualitatively different effects at low concentrations, and quantitatively different ones at high concentrations. This is a quite complex and perhaps not so rare example of enantioselectivity seen in the functional test of an ion channel-linked receptor, and it aptly illustrates situations where logic and decision trees are found wanting.

STEREOSELECTIVITY IN UNWANTED EFFECTS?

Whether stereoselectivity in principal activity exists or not, stereoselectivity in unwanted effects seems the



I II III



IV V VI

next logical question to ask. Here, even a slight difference in toxicity may be sufficient to conclude that the racemate is not marketable as such. A glaring and tragic example (how easy it is to be wise after the event!) is that of thalidomide. As critically reviewed by De Camp,[18] the two enantiomers of thalidomide have similar hypnotic effects, whereas the teratogenic effects appear ascribable to the S-enantiomer.

Again not all documented cases are straightforward, and opinions may diverge about the meaning of unwanted effects. In particular, unwanted reactions can be detected at the molecular level (e.g., lipoperoxidation, covalent binding, inhibition of physiological reactions) which may or may not be connected to toxic symptoms but should always be a consequential cause of concern. Thus, antiinflammatory 2-arylpropionates (profens) exist as eutomers of S configuration and distomers of R configuration. Interestingly, the distomers of some of these drugs, but not their eutomers, form hybrid triglycerides.[19] These are abnormal and long-lasting metabolites of potentially serious toxicological significance. Furthermore, some distomeric profens, but not their eutomers, inhibit the mitochondrial β-oxidation of fatty acids, a molecular event possibly accounting for microvesicular steatosis.[20]

STEREOSELECTIVITY IN OTHER WANTED EFFECTS?

Assuming acceptably low toxicity of both enantiomers of a given drug, one could now conclude that development and marketing of the racemate are justified. However, a careful scientist will want to further understand the pharmacodynamic and pharmacokinetic behaviour of the separate enantiomers, as well as possible interactions between them.

Besides their principal activity and unwanted effects, drugs may display additional effects that may contribute favourably to the overall therapeutic response. For example, carvedilol is a potent, competitive antagonist of β_1-adrenoceptors, the activity residing practically exclusively in the (−)-(S)-eutomer. In contrast, both enantiomers of carvedilol produced an equal, and marked, blockade of α_1-adrenoceptors.[21] It follows that *rac*- and (S)-carvedilol differ in the molecular mechanisms by which they elicit antihypertensive effects, and that either *rac*- or (S)-carvedilol should be selected depending on the desired therapeutic profile.

PHARMACOKINETIC OR PHARMACODYNAMIC INTERACTIONS BETWEEN STEREOISOMERS?

Even if a distomer is essentially biologically inert with respect to both the desired therapeutic effect and any unwanted side effects, still another level of potential interaction must be considered before an informed decision can be reached regarding development and marketing of eutomer or racemate. The inherent activity of a drug, while primary, is not the only parameter that determines the ultimate response of a biological system to that drug. Of equal importance are its rate of elimination from the organism, since this determines exposure time, and its distribution within the organism, since this determines whether or not the drug reaches the site of action and in what concentration. Insofar as the distomer can alter either the intrinsic rate of elimination or the intrinsic distribution of the eutomer, it will modulate biologic response.

While there are not overwhelming numbers of examples in the literature that document enantiomeric interactions, there is no a priori reason to assume that they are rare events. Even though stereochemical phenomena have been recognized for more than a century it is only within the last decade that a general appreciation for their importance in therapeutics has developed along with the methodology necessary for their study.

An example of one of the best recognized enantiomeric interactions is that between the enantiomers of the β-blocker propranolol (V). In 1972, George et al.[22] reported that the half-life of (R)-propranolol in humans was shorter when given alone than as the racemate. The discrepancy in half-life is believed to be due to the fact that racemic propranolol decreases hepatic blood flow while (R)-propranolol alone does not. Since the clearance of a drug with high extraction ratio, e.g., propranolol, is expected to be limited by hepatic blood flow the half-life of (R)-propranolol should indeed increase when it is administered as the racemate.

A second example is provided by the antiarrhythmic agent disopyramide (VI), whose enantiomers display a complex pharmacokinetic interaction.[23] Indeed, the *dextro*-enantiomer, when administered in the racemate had a lower plasma and renal clearance, a longer half-life, and a smaller apparent volume of distribution than the *laevo*-enantiomer. However, when the two enantiomers were administered separately there were no differences between them in any of these pharmacokinetic parameters.

As a final example, recent work from the School of Pharmacy, University of Washington, will be considered (K.L. Kunze, A.C. Eddy, M. Gibaldi, and W.F. Trager, unpublished results). In studies designed to probe the possibility of establishing an approach to in vitro–in vivo metabolic correlations, the effects of inhibitors on the formation clearances of warfarin in vitro and in vivo were investigated.[24] During the course of these studies, it was found that with human liver microsomes (R)-warfarin is a potent and selective competitive inhibitor of the 7-hydroxylation of (S)-warfarin even though it, itself, is not a substrate for the cytochrome P-450 isozyme catalyzing the reaction. In the three human livers examined the K_i values for (R)-warfarin inhibition of (S)-warfarin 7-hydroxylation ranged from 6 to 8.5 μM while the K_m values of the reaction ranged from 3.7 to 4.7 μM. Since the termination of the pharmacological effect of *rac*-warfarin during anticoagulant therapy is primarily due to the processing of the more potent S-enantiomer by the (S)-7-hydroxylase to (S)-7-hydroxywarfarin and since (R)-warfarin is a potent inhibitor of this process, having a K_i of almost equal magnitude to the K_m for (S)-

warfarin, the administration of *rac*-warfarin might be expected to lead to a significantly longer half-life for (S)-warfarin (together with a corresponding increase in biological activity) than would be the case had (S)-warfarin been administered separately. This supposition assumes of course that the free concentrations of the two warfarin enantiomers, following administration of therapeutic doses, reach hepatic levels that are sufficient to allow the interaction to become significant and observable. Whether or not this is indeed the case is currently under investigation.

CONCLUSION

What we hope to provide in this discussion is a balanced view of the issues surrounding the use of racemic drugs and to develop a logical and informed strategy for the decisions that must be reached in the development of new medicinal agents. Much of the debate has seemed to center around the possibility that the eutomer might possess most of the therapeutic value of a given chiral drug while the distomer is responsible for most of the toxic liability, e.g., the tragic case of thalidomide. Or, the eutomer might have all of the therapeutic activity while the distomer is virtually inactive and therefore of no value. However, a point of view that appears not to have been as forcefully expressed is the notion that the presence of both enantiomers may provide a distinctly superior therapeutic agent than would be realized by the administration of the eutomer alone. For example, it is possible that a distomer might either inhibit the formation of a toxic metabolite from the eutomer or decrease its clearance such that the dose of eutomer required to achieve the desired response can be lowered.

While it is abundantly clear that a racemic mixture must be considered as the mixture of two pharmacologically distinct entities, it is also clear that this view, in and of itself, does not infer any value judgment. Such judgment awaits the light of scientific fact and it is only in this context that any decision as to develop a racemate or a eutomer as a new drug is convincingly founded.

ACKNOWLEDGMENTS

This work was supported in part by the Swiss National Science Foundation (H.T.) and by National Institutes of Health Program Project Grant GM 32165 (W.F.T.).

LITERATURE CITED

1. Lehmann, P.A. Stereoisomerism and drug action. Trends Pharmacol. Sci. 7:281–285, 1986.
2. Lehmann, P.A. A quantitative stereostructure activity relationship analysis of the binding of pronuncious chiral ligands to different receptors. Quant. Struct.-Act. Relat. 6:57–66, 1987.
3. Ariëns, E.J. Stereochemistry, a basis for sophisticated nonsense in pharmacokinetics and clinical pharmacology. Eur. J. Clin. Pharmacol. 26:663–668, 1984.
4. Ariëns, E.J. Stereochemistry: A source of problems in medicinal chemistry. Med. Res. Rev. 6:451–466, 1986.
5. Testa, B. Chiral aspects of drug metabolism. Trends Pharmacol. Sci. 7:80–84, 1986.
6. Testa, B. Substrate and product stereoselectivity in monooxygenase-mediated drug activation and inactivation. Biochem. Pharmacol. 37:85–92, 1988.
7. Testa, B. Principles of Organic Stereochemistry. New York: Dekker, 1979: 44–48.
8. Aso, Y., Yoshioka, S., Shibazaki, T., Uchiyama, M. The kinetics of the racemization of mazepam in aqueous solution. Chem. Pharm. Bull. 36:1834–1840, 1988.
9. Yang, S.K., Lu, X.-L. Racemization kinetics of enantiomeric mazepams and stereoselective hydrolysis of enantiomeric mazepam 3-acetates in rat liver microsomes and brain homogenates. J. Pharm. Sci. 78:759–795, 1989.
10. Testa, B. Some chemical and stereochemical aspects of diethylpropion metabolism in man. Acta. Pharm. Suec. 10:441–454, 1973.
11. Eveleigh, P., Bulbne, P.C., Schadk, C., Birdsall, N.J.M. The existence of stable enantiomers of telenzepine and their stereoselective interaction with muscarinic receptor subtypes. Mol. Pharmacol. 35:477–483, 1989.
12. Pfeiffer, C.C. Optical isomerism and pharmacological action, a generalization. Science 126:29–31, 1956.
13. Testa, B. Definitions and concepts in biochirality. In: Chirality and Biological Activity. Holmstedt, B., Frank, H., Testa, B., eds. New York: Liss, 1990: 15–32.
14. Barlow, R.B., Franks, F.M., Pearson, J.D.M. The relation between biological activity and the degree of optical resolution of optical isomers. J. Pharm. Pharmacol. 24:753–761, 1972.
15. Breckenridge, A., L'Orme, M., Wesseling, H., Lewis, R.J., Gibbons, R. Pharmacokinetics and pharmacodynamics of the enantiomers of warfarin in man. Clin. Pharmacol. Therap. 15:424–440, 1974.
16. Jähnchen, E., Meinertz, T., Gilfrich, H.J., Groth, U., Martini, A. The enantiomers of phenprocoumon: Pharmacodynamics and pharmacokinetic studies. Clin. Pharmacol. Therap. 20:342–349, 1976.
17. Conte-Camerino, D., Mambrini, M., Delaco, A., Tricarico, D., Bryant, S.H., Tortorella, V., Bettoni, G. Enantiomers of clofibric acid analogs have opposite actions on rat skeletal muscle chloride channel. Eur. J. Physiol. 413:105–107, 1988.
18. De Camp, W.H. The FDA perspective on the development of stereoisomers. Chirality 1:2–6, 1989.
19. Williams, K., Day, R., Knihinicki, R., Duffield, A. The stereoselective uptake of ibuprofen enantiomers into adipose tissue. Biochem. Pharmacol. 36:3401–3406, 1988.
20. Geciova, J., Hayat-Bosan, H., Labbé, G., Degott, C., Letteron, P., Fromenty, E., Le Dinh, T., Larrey, D., Pessayre, D. Inhibition of mitochondrial β-oxidation of fatty acids by pirprofen. Role in microvesicular steatosis due to this non-steroidal anti-inflammatory drug. J. Pharmacol. Exp. Ther. 242:1133–1137, 1987.
21. Nichols, A.J., Salgado, A.C., Ashton, D.J., Hubble, J.P., Ruffolo, R.R., Jr. The interaction of the enantiomers of carvedilol with α- and β-adrenoceptors. Chirality 1:265–270, 1989.
22. George, C.F., Fenyvesi, C., Connolly, M.E., Dollery, C.T. Pharmacokinetics of dextro, laevo and racemic propranolol in man. Eur. J. Clin. Pharmacol. 5:485–490, 1972.
23. Giacomini, K.M., Nelson, W.L., Perchalski, R.J., Yaldiviezo, L., Turner-Tamiyasu, K., Blaschke, T.F. In vivo interaction of the enantiomers of disopyramide in human subjects. J. Pharmacokinet. Biopharm. 14:335–358, 1986.
24. Rettie, A.E., Eddy, A.C., Hermark, L.D., Gibaldi, M., Trager, W.F. Characteristics of warfarin hydroxylation catalyzed by human liver microsomes. Drug Metab. Disp. 17:265–270, 1989.

Exhibit B

0701.0354

United States Patent [19]
Sunshine et al.

[11] Patent Number: 4,851,444
[45] Date of Patent: Jul. 25, 1989

[54] ONSET-HASTENED/ENHANCED ANALGESIA

[75] Inventors: Abraham Sunshine, New York; Eugene M. Laska, Larchmont, both of N.Y.

[73] Assignee: Analgesic Associates, Larchmont, N.Y.

[21] Appl. No.: 71,914

[22] Filed: Jul. 10, 1987

[51] Int. Cl.⁴ A61K 31/19
[52] U.S. Cl. 514/570; 514/557; 514/960; 514/962; 514/947
[58] Field of Search 514/557, 570

[56] References Cited

U.S. PATENT DOCUMENTS

4,355,524 11/1985 Gruber et al. 514/570
4,690,823 9/1987 Lolger et al. 514/570

FOREIGN PATENT DOCUMENTS

0267221 5/1988 European Pat. Off. .

OTHER PUBLICATIONS

Biochemical Pharmacology, vol. 35, No. 19 (Oct. 1986), pp. 3403–3405, Pergamon Journals Ltd., K. Williams et al., "The Stereoselective Uptake of Ibuprofen Enantiomers into Adipose Tissue".
Current Medical Research and Opinion, vol. 3, No. 8 (1975), p. 552, S. S. Adams et al., "The Optical Isomers of Ibuprofen".
J. Pharm. Pharmacol., vol. 28 (1976), pp. 256–257, S. S. Adams et al., "Pharmacological Difference Between the Optical Isomers of Ibuprofen: Evidence for Metabolic Inversion of the (—)—Isomer".
Journal of Pharmaceutical Sciences, vol. 56 (1967), p. 1686, S. S. Adams et al., "Some Biological Properties of 2—(4—Isobutylphenyl)—Propionic Acid".
Biochemical and Biophysical Research Communications, vol. 61, No. 3 (1974), pp. 833–837, W. J. Wechter et al., "Enzymatic Inversion at Saturated Carbon: Nature and Mechanism of the Inversion of R(—)-α—Methyl-4-Butyl Hydratropic Acid".
J. Pharm. Pharmacol., vol. 35 (1983), pp. 693–704, Andrew J. Hutt et al., "The Metabolic Chiral Inversion of 2—Arylpropionic Acids—A Novel Route with Pharmacological Consequences".
Clinical Pharmacokinetics, vol. 9 (1984), pp. 371–373, Andrew J. Hutt et al., "The Importance of Stereo—Chemistry in the Clinical Pharmacokinetics of the 2–Arylpropionic Acid Non-Steroidal Anti-Inflammatory Drugs".
The Journal of Pharmacology and Experimental Therapeutics, vol. 232, No. 3 (1985), pp. 636–643, J. W. Cox et al., "Ibuprofen Stereoisomer Hepatic Clearance and Distribution in Normal and Fatty in Situ Perfused Rat Liver".
Clinical Pharmacology & Therapeutics, vol. 41, No. 2 (Feb. 1987), p. 200.
Clinical Pharmacology & Therapeutics, vol. 40, No. 1 (1986), pp. 1–7, Eugene M. Laska et al., "The Correlation Between Blood Levels of Ibuprofen and Clinical Analgesic Response".
Chemical Abstracts, vol. 106 (1987), Abstract No. 66922r (Daicel Chemical Industries, Ltd.).
Physicians' Desk Reference, 40th Edition (1986), pp. 1854–1855, Edward R. Barnhart.
Xenobiotica, vol. 3, No. 9 (1973), pp. 589–598, R. F. N. Mills et al., "The Metabolism of Ibuprofen".
Journal of Pharmaceutical Sciences, vol. 64, No. 5 (1975), pp. 798–801, Garret J. Vangiessen et al., "GLC Determination of Ibuprofen [dl–2–(p–Isobutylphenyl)–Propionic Acid] Enantiomers in Biological Specimens".
Journal of Pharmaceutical Science, vol. 65, No. 2 (Feb. 1976), pp. 269–273, D. G. Rauer et al., "Isomeric Inversion of Ibuprofen (R)–Enantiomer in Humans".
Anti-Inflammatory and Anti-Rheumatic Drugs, Eds. Rainsford and Path, CRC Press Inc., Boca Raton, Fla. (1985), p. 172, Anthony C. Allison et al., "Naproxen".
Angew. Chem. Internat. Edit., vol. 11, No. 6 (1972), pp. 460–472, T. Y. Shen, "Perspectives in Nonsteroidal Anti-Inflammatory Agents".
Nonsteroidal Anti-Inflammatory Agents, Chapter 62 in Burger's Medical Chemistry, 4th Edition, Part III, Wiley Interscience, New York (1981), pp. 1205–1271, T. Y. Shen.
Br. J. Clin. Pharmac., vol. 18 (1985), pp. 669–674, E. J. D. Lee et al., "Stereoselective Disposition of Ibuprofen Enantiomers in Man".
The Journal of Pharmacology and Experimental Therapeutics, vol. 148, No. 3 (1965), pp. 373–379, Charles A. Winder et al., "Nociceptive Thresholds as Affected by Parenteral Administration of Irritants and of Various Antinociceptive Drugs".
Proceedings of the Society for Experimental Biology and Medicine, vol. 118, (1965), pp. 762–766, H. Blumberg et al., "Use of Writhing Test for Evaluating Analgesic Activity of Narcotic Antagonists".
Journal of Pharmaceutical Sciences, vol. 73, No. 11 (Nov. 1984), pp. 1542–1544, E. J. D. Lee et al., American Pharmaceutical Association, "Liquid Chromatographic Determination and Plasma Concentration Profile of Optical Isomers of Ibuprofen in Humans".
Remington's Pharmaceutical Sciences, 15th Edition (1975), Mack Publishing Company, Easton, Pennsylvania 18042, Chapter 59, p. 1054, John E. Hoover.
Caldwell et al., "The Metabolic Chiral Inversion and Dispositional Enantioselectivity of the 2–Arylpropionic Acids and Their Biological Consequences", vol. 37, No. 1, pp. 105–116 (1988).

Primary Examiner—Jacqueline V. Howard
Attorney, Agent, or Firm—Burns, Doane, Swecker & Mathis, LP

[57] ABSTRACT

Onset-hastened and enhanced analgesic response is elicited in a mammalian organism in need of such treatment, i.e., a mammal suffering pain, by administering thereto a unit dosage onset-hastening/enhancing analgesically effective amount of the S(+) ibuprofen enantiomer, said enantiomer being substantially free of its R(—) ibuprofen antipode.

39 Claims, No Drawings